. REMARKS

INTRODUCTORY COMMENTS:

Claims 83-87 were pending and at issue and were examined in the Office Action dated September 9, 2004. These claims, and those of related applications having serial nos.09/295,463, and 10/116,325 were discussed with the Examiner in a telephonic interview conducted December 21, 2004. The amendments to the claims are made to distinguish Applicants' invention from the primary reference, Agrafiotis, *et al.* (USPN 5,463,564) in light of the interview discussion. During the interview, Applicants' representatives highlighted a distinguishing feature between the instant invention and Agrafiotis, *et al.*, i.e., that Agrafiotis, *et al.* relies on synthesis and testing of a directed diversity library (*see* Agrafiotis, *et al.* at Col. 5, lines 31-45; Col. 22, lines 13-40) to produce information for a structure-activity relation database (*see* Agrafiotis, *et al.* at Fig. 2; Col. 5, lines 56-64), and only after synthesis and testing, does Agrafiotis begin to refine the universe of compounds, although that refinement is achieved by synthesizing additional compounds. *See* Agrafiotis, *et al.* at Fig. 2; Col. 6, lines 49-53; Col. 22, lines 41-67; Col. 23, lines 1-30.

The instant claimed invention takes a different tack for solving the problem of identifying active compounds. Applicants' claimed invention relies on a computer system that uses defined criteria to eliminate sequences from a larger set of virtual compounds. Only after such reduction is accomplished, are actual compounds synthesized. The Examiner indicated that because Applicants' claim language is open, the claims failed to distinguish over Agrafiotis' step of synthesizing and testing compounds prior to eliminating *in silico* compounds from a larger set.

Applicants have amended the claims to distinguish the instant invention from Agrafiotis' method

in an earnest effort to advance prosecution, as explained in greater detail below.

STATUS OF THE CLAIMS

Claims 83-87 were pending in this application. Claims 83, 85, 86, and 87 have been

amended. Following entry of the amendments claims 83-87 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claims 83, 85, 86, and 87 are amended to recite:

> a computer system that prepares a virtual
> library of oligonucleotide[s] sequences targeted
> to said selected nucleic acid and generates
> synthesis instructions in computer manipulable
> form for [each of]said oligonucleotide[s]
> sequences in said virtual library, wherein said
> computer system first prepares said virtual library
> of oligonucleotide sequences and then reduces the
> number of oligonucleotide sequences in
> [members of]said virtual library of
> oligonucleotide[s] sequences by ...;

> an automated synthesizer that receives
> said synthesis instructions from said computer
> system and synthesizes only that [a]set of real
> oligonucleotides that corresponds
> [corresponding]to said virtual set of
> oligonucleotide[s] sequences [having]consisting
> of said reduced number of oligonucleotide
> sequences[members] ...

to more clearly define Applicant's invention and to distinguish the claimed invention from

Agrafiotis *et al.*, USPN 5,463,564. Support for the amendments can be found throughout the

specification as filed, at, e.g., 19:10-25; 22:33 – 23:10; 24:34 – 26:22; 65:25 – 66:22; 89:2 –

94:4; 103:16 – 105:18; Figures 1, 4, 5, 20 and 22.

REJECTIONS OF THE CLAIMS UNDER 35 U.S.C. §103

(a)   The Examiner has maintained the rejection of claims 83 and 85-87 under 35 U.S.C.

§103(a) as allegedly being unpatentable over U.S. Patent No. 5,463,564 to Agrafiotis, *et al.* in

view of Hyndman, *et al.* (1996) Biotechniques 20(6): 1090-1094 further in view of Nickerson, *et al.* (1990) Proc. Nation. Acad. Scien. 87: 8923.

Applicants have amended claims 83, 85, 86, and 87 to distinguish the claimed invention from Agrafiotis *et al.* USPN 5,463,564. As discussed during the telephonic interview conducted December 21, 2004, Applicants' claimed invention differs from Agrafiotis, *et al.* because Agrafiotis, *et al.* describes generating a directed diversity chemical library where the number of compounds must increase with each iteration since additional compounds are synthesized for a new directed diversity chemical library. Further, at no point does the reference, alone or in combination with the secondary references, describe creating a virtual library of oligonucleotides, and then reducing the number of members in the virtual library using the criteria recited in the instant claims, followed by synthesis of only those compounds that remain following the reduction step. Instead, Agrafiotis, *et al.* teaches synthesizing and testing all members of the library as actual compounds once the chemical building blocks are selected. In the Agrafiotis process, initialization occurs by selecting a particular set of chemical building blocks "aimed at maximizing the information content of the resulting chemical library." Col. 16, lines 64-66. Once selected, the selected building blocks are combined to physically synthesize all combinations of the compounds (Col. 5, lines 31-45; Col. 22, lines 13-40). Thus, Agrafiotis physically synthesizes all compounds during initialization so that the number of oligonucleotide sequences in a virtual library is not reduced prior to synthesis. The synthesized compounds are analyzed to obtain structure-activity data (SAR) (Fig. 2; Col. 5, lines 56-64), and the collected SAR and historical SAR are subsequently used to synthesize additional compounds for a new directed diversity chemical library (Fig. 2; Col. 6, lines 49-53; Col. 22, lines 41-67; Col. 23, lines 1-30).

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In contrast, Applicant's claimed invention (as amended) relies on "a ... system [that] first prepares said virtual library of oligonucleotide sequences and then reduces the number of oligonucleotide sequences in [members of]said virtual library of oligonucleotide[s] sequences, and instructs an automated synthesizer that "synthesizes only that [a]set of real oligonucleotides that corresponds [corresponding]to said virtual set of oligonucleotide[s] sequences [having]consisting of said reduced number of oligonucleotide sequences[members] . . ."

Contrary to Agrafiotis, et al., Applicant's claimed invention (as amended) prepares a virtual library of oligonucleotide sequences consisting of, for example X sequences, reduces the number of oligonucleotide sequences in the virtual library, and instructs an automated synthesizer that synthesizes a set of real oligonucleotides consisting of, for example Y sequences, so that, Y is less than X as a consequence of the reduction step.

Furthermore, Applicants respectfully submit that the proposed modification to Agrafiotis, et al. is improper because it renders Agrafiotis, et al. unsatisfactory for its intended purpose. Agrafiotis' invention relies on synthesizing and collecting data using a set of compounds, followed by iteration and synthesis of additional compounds based on structure activity relationship data obtained from the initial set. As the Agrafiotis, et al. specification teaches, an initial set of building blocks is selected for making a directed diversity library. Those building blocks are selected to provide maximum information content:

> The initial choice is aimed at maximizing the information content of the resulting chemical library within the domain of interest, as measured by the presence of chemical functionalities, hydrogen bonding characteristics, electronic properties, topological and topographical parameters.

'564 at Col. 16, lines 64-17:2.

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As the Examiner already has agreed, once the building blocks are selected, Agrafiotis

teaches synthesizing all combinations of the building blocks to make up the initial directed

diversity library (*see, e.g.,* '546 at Col. 22, lines 12-34). The compounds then are screened for

the property of interest and the resulting data is used for three purposes:

> In a preferred embodiment of the present
> invention, the highest-ranking models identified
> in step 602 are used in step 608 to select a set of
> compounds which, as a set, best satisfy the
> following requirements: (1) exhibit improved
> activity as predicted by the highest ranking
> structure-activity models; (2) test the validity of
> the highest ranking structure-activity models,
> and/or (3) discriminate between the highest
> ranking structure-activity models. Requirements
> (2) and (3) allow for the selection of compounds
> which need not necessarily exhibit improved
> activity but, rather, prove or disprove some of the
> highest ranking structure-activity models, or
> discriminate most effectively between them.

'564 at Col. 18, lines 52-64.

Because the proposed modification to reduce *in silico* the members of the directed

diversity library according to the criteria identified in the instantly claimed invention interferes

with Agrafiotis' requirement to derive structure-activity models having enhanced predictive and

discriminating capabilities it renders Agrafiotis unsatisfactory for its intended purpose. The

motivation therefore is improper. *See* MPEP Section 2143.01.

Further, Hyndman, *et al.* does not cure the above-noted deficiencies in Agrafiotis, *et al.*

because, Hyndman, *et al.*, alone or in combination with Agrafiotis, *et al.* and Nickerson, *et al.*

fails to teach or suggest all claim elements. Hyndman, *et al.* teaches a computer program

(HYB*simulator*) that uses input criteria such as melt temperature, free energy and length to

design a probe set against a target sequence, but then identifies preferred probes by eliminating

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sequences with insufficient target specificity (pp. 1092, 1094, and Figure 4), or retaining probes

expected to perform well in PCR amplifications. The Hyndman process does not teach or

suggest reducing the number of oligonucleotide sequences in a virtual library using a process of

selection based on targeting a functional region of said selected nucleic acid as required by the

amended claim 83, nor reduction by one or more of i) a process of selection based on target

accessibility to said selected nucleic acid, ii) a process of selection based on uniform distribution

of oligonucleotide compounds across said selected nucleic acid, or iii) a process of selection

based on targeting a functional region of said selected nucleic acid as required by amended

claims 85-87. Thus, Hyndman, alone or in combination with the primary Agrafiotis, *et al.*

reference, does not teach or suggest all the elements of the claimed invention.

The Examiner states that Hyndman's probes are target specific and that target specificity

is a functional characteristic of the probes. Probes that are specific for a target are not the same

as oligonucleotides that are designed for the functional regions of the target. Probes that are

specific to a target are selected on the basis of homology to regions of target sequence that are

not found within non-targets sequences. Accordingly a probe designed to hybridize specifically

to a particular target does not necessarily target a functional region. Thus, a process of reducing

the number of members of a virtual library of oligonucleotide sequences based on target

specificity criteria does not explicitly or inherently teach a process based on targeting a functional

region nor does it teach the other two processes of claims 85-87.

Nickerson *et al.* merely describe the testing of oligonucleotides using automated

apparatus.

Thus, the combination of Agrafiotis *et al.,* Hyndman *et al.* and Nickerson *et al.* does not

disclose reducing the number of members of a virtual library of oligonucleotides based on i) a

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process of selection based on target accessibility to said selected nucleic acid, ii) a process of selection based on uniform distribution of oligonucleotide compounds across said selected nucleic acid, or iii) a process of selection based on targeting a functional region of said selected nucleic acid. The combination of the cited references does not disclose all the elements of the claims 83 and 85-87 as currently amended, and the Examiner is respectfully requested to withdraw the rejection.

(b)   The Examiner has maintained the rejection of claims 83-87 under 35 U.S.C. §103(a) as allegedly being unpatentable over Agrafiotis, *et al.* in view of Hyndman, *et al.* and Nickerson *et al.* further in view of U.S. Patent No. 5,352,775 to Albertsen, *et al.* or U.S. Patent No. 5,407,796 to Cutting, *et al.*

The applicants traverse the rejection by way of amendment and argument. Agrafiotis *et al.,* Hyndman, *et al.* and Nickerson, *et al.* are discussed above. Albertsen and Cutting were cited for desirability of certain target nucleic acid regions. The combination of Agrafiotis, *et al.* in view of Hyndman, *et al.* and Nickerson, *et al.* further in view of Albertsen, *et al.* or Cutting, *et al.* does not disclose reducing the number of members of a virtual library of oligonucleotides based on i) a process of selection based on target accessibility to said selected nucleic acid, ii) a process of selection based on uniform distribution of oligonucleotide compounds across said selected nucleic acid, or iii) a process of selection based on targeting a functional region of said selected nucleic acid. Thus, the combination of Albertsen, *et al.* or Cutting, *et al.* with Agrafiotis, *et al.,* Hyndman, *et al.* and Nickerson, *et al.* does not teach or suggest the claimed methods in which the number of oligonucleotides synthesized is reduced using the defined criteria. Because the claims as amended distinguish the invention over the cited references, the Examiner is respectfully requested to withdraw the rejection.

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PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 83 and 85-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55, 56, 58-72, 74-87, and 99-102 of copending Application No. 09/295,463. Applicants agree to execute a terminal disclaimer upon indication of allowable subject matter in the referenced and instant applications.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicants' representative at (415) 875-2413.

Respectfully submitted,
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